REMARKS

Claims 1-13 and 15-21 are pending. Applicants have cancelled claim 15 without prejudice and have added new claims 22-27. Claims 1-13 and 16-27 will therefore be pending upon entry of the proposed amendments.

Applicants have deleted the terms "solvate" in claims 1, 11-13, and 16-21 and "solvates" in claim 10.

Support for new claims 22-27 can be found throughout the specification, for example, at page 7, lines 14, 26-27, and 31, at page 8, lines 7, 11, 13, 15, and 26-28, at page 9, lines 2-3, and at page 10, lines 1-3, 5-6, 12-13, and 16-17; and the exemplified compounds disclosed at page 22, line 1 through page 54, line 26.

No new matter is introduced by these amendments.

The foregoing amendments are being made for the sole purpose of expediting prosecution of the present application, and applicants expressly reserve the right to pursue any cancelled subject matter in a later filed continuing application.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-13 and 16-21 are rejected for allegedly failing to comply with the enablement requirement of 35 U.S.C. §112, first paragraph.

I. The rejection states, in part (Office Action, page 3):

> In regard to lack of enablement issue of instant claims 1-13 and 15-21 for solvates of instant compounds of formula (I), there is no teaching or guidance present in the specification for preparing any specific solvates.

The rejection of claim 15 is moot in view of its cancellation.

Applicants respectfully disagree with the grounds for the rejection; however to expedite prosecution, Applicants have deleted the terms "solvate" in claims 1, 11-13, and 16-21 and "solvates" in claim 10. Applicants respectfully request reconsideration and withdrawal of the rejection in view of the foregoing amendments.

II. Claims 15-21 are also rejected on a separate ground. The rejection states, in part (Office Action, page 3, emphasis added):

> There is no teaching in the prior art that structurally closely related compounds having antagonist activity at MIP-1 alpha receptors are well known to have therapeutic activity in treating all disease conditions mentioned in instant claims 15-21. <u>There are no working examples present showing efficacy of instant compounds in known animal models of rheumatoid arthritis, COPD, asthma, multiple sclerosis, any inflammatory disease or any airway disease</u>. The instant compounds of formula (I) encompasses hundreds of thousands of compounds based on the values of variables R^1-R^5, n, m, p, q, t, X and Y and therefore, in absence of such teachings, guidance, presence of working examples and prior art, it would require undue experimentation to demonstrate efficacy of instant compounds in known animal models of rheumatoid arthritis, COPD, asthma, multiple sclerosis, every known inflammatory disease, every known airway disease and hence their utility for treating these disorders.

The rejection of claim 15 is moot in view of its cancellation.

Applicants respectfully request reconsideration and withdrawal of the rejection in view of the following remarks.

[1] Applicants first wish to address the underlined portion in the above-quoted passage from the Office Action. There is no legal requirement that the specification include biological data for the claimed compounds (in fact, there is no legal requirement that the specification provide working examples at all). Further, it is well settled that the standard for patentability is very different than that for FDA approval or clinical acceptance. One can enable a claim of treating cancer without, e.g., having FDA approval or clinical acceptance of the method. See *In re Brana*, 34 USPQ2d 1436, 1444, *Scott v. Finney*, 32 USPQ2d 1115,1120.

[2] The Federal Circuit discussed the purpose of the enablement requirement of 35 U.S.C. § 112, first paragraph in *Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.* 418 F.3d 1326, 1336-1337 (2005) (underline emphasis added):

> The purpose of this requirement is to ensure that 'the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims.' *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed.Cir.1999); *see also* Donald S. Chisum, 3 *Chisum on Patents* § 7.01 (2002).

The Federal Circuit in *Warner-Lambert* stressed that the specification must teach one how to make and use the claimed invention without undue experimentation (*Id.* at 1337, underline emphasis added):

> Accordingly, we have held that the specification must provide sufficient teaching such that one skilled in the art could make and use the full scope of the invention without undue experimentation. *[citation omitted]* 'The key word is 'undue,' not experimentation.'' *Wands,* 858 F.2d at 737 (citation omitted). That is, the specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. *See, e.g., Nat'l Recovery Techs.*, 166 F.3d at 1196 ('The scope of enablement ... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.'); *Wands,* 858 F.2d at 736-37 ('Enablement is not precluded by the necessity for some experimentation such as routine screening.').

The specification teaches a genus of compounds having formula (I) that are capable of modulating chemokine receptor activity ("especially MIP-1α chemokine receptor" see specification at page 17, line 32). Such compounds are claimed in claim 1, which the Office has indicated is allowable (Office Action, page 5). In addition:

[A] The specification teaches one how to both synthesize and administer the claimed compounds (specification at page 14, line 1 through page 17, line 18; page 20, lines 4-32; and the 20 synthesis examples beginning at page 22). The specification also provides an art recognized *in vitro* assay (THP-1 Chemotaxis Assay) that can be used to evaluate the claimed compounds'

ability to modulate MIP-1α chemokine receptor activity. As taught in the specification(specification at page 55, lines 4-6):

> The assay measures the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. Compounds are evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

Chemokines, chemokine receptors, the MIP-1α chemokine receptor (as well as the other chemokine receptors discussed in the specification), and the aforementioned biological assay were known in the art as of Applicants' filing date.

[B] The specification teaches, for example, that the claimed compounds have activity as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity:

> The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

As further evidence of this, Applicants provide biological data that was obtained by testing the 20 compounds exemplified in the specification (see Appendix A). More specifically, the data shows the IC_{50} values exhibited by each of the exemplified compounds in a Human Recombinant CCR1 Binding Assay. As can be seen, the majority of the tested compounds exhibited IC_{50} values, that is the molar concentration of compound producing 50% displacement of labeled [^{125}I]MIP-1α, in the low micromolar to sub-nanomolar range.

The Office, which appears to acknowledge the claimed compounds' ability to modulate MIP-1α chemokine receptor activity, has provided no evidence why an observed *in vitro* effect would fail to show predictability of this effect in the body or would somehow not be relevant to predicting the compounds' ability to treat the claimed disorders.

[C] The nexus between (1) modulating chemokine receptor activity ("especially MIP-1α chemokine receptor activity); and (2) autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases (which encompass the specifically claimed disorders), and the treatment of the above-mentioned diseases was established as of Applicants' filing date. This is discussed, e.g., in detail in the Background[1] section of the specification. Since the claimed compounds are capable of modulating chemokine receptor activity ("especially MIP-1α chemokine receptor activity"), the skilled artisan at the time of filing would have reasonably predicted that the claimed compounds would have been useful for treating, at the very least, the disorder recited in claims 16-21.

[3] The Federal Circuit in *In re Wright* 27 USPQ2d 1510, 1513 (1993) discussed the requirements for rejecting a claim under the enablement requirement of 35 U.S.C. § 112, first paragraph (underline emphasis added):

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

Applicants submit that the Office has not met this burden because, at the very least, the Office has not identified any aspect of the claimed methods that a person of ordinary skill in the art "could not figure out without undue experimentation" (*Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.* 418 F.3d 1337). The skilled artisan could evaluate the ability of Applicants' novel and unobvious claimed compounds to treat rheumatoid arthritis, COPD, asthma, inflammatory disease, airways disease, or multiple sclerosis, by synthesizing a candidate compound of the claims and subjecting that compound to an art-recognized assay for treating

---

[1] The Federal Circuit in *Callicrate v. Wadsworth Mfg., Inc.* 427 F.3d 1361, 1374 (2005) held that the background sectin of a patent specification can enable a feature of a claimed invention: "First, a patent specification may sufficiently enable a feature under § 112, paragraph 1, even if only the background section provides the enabling disclosure."

that particular disease. Of course, this is **not** to say that the specification does not establish a nexus between the claimed compounds and the treatment of the diseases recited in claims 16-21. Rather, establishing the nexus apparently sought by the Office falls within the purview of routine screening, which in and of itself does not preclude enablement (*see Wands*, 858 F.2d at 736-737).

[4] Finally, the Specification teaches that the claimed compounds, which all share common and substantial structural attributes, can modulate chemokine receptor activity. A person of ordinary skill in the art would therefore have reasonably expected Applicants' nondisclosed variants to have had this activity as well. The Office has provided no specific evidence that Applicants' contemplated variations within formula (I) would render the claimed compounds inoperable for their intended purpose. That being said, even if one or more of the claimed compounds were found to be inactive (and Applicants do not concede that this is the case here), that does not render the claims unpatentable. The claims need not exclude inoperative embodiments. As the Federal Circuit explained in *Atlas Powder Co. v. E. I. Du Pont De Nemours & Co.* 224 USPQ 409 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude ... possible inoperative substances..." *Atlas Powder* at 414.

In any event, to enable a claim to a genus, one need **not** disclose and test every species encompassed by the genus, even in the so-called unpredictable arts. To require as such would limit the Applicants merely to what he or she has already done. Again, this is not the law. *See, e.g., In re Angstadt*, 190 USPQ 214, (CCPA 1976). See also MPEP § 2164.02: "[b]ut because only an enabling disclosure is required, applicant need not describe all actual embodiments."

Thus, the specification provides sufficient teaching such that a person of ordinary skill in the art could practice the claimed methods without undue experimentation. In view of the foregoing, Applicants respectfully request that the 35 U.S.C. § 112, first paragraph rejection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claim 6 is rejected for allegedly being indefinite because the claim does not end with a period. This rejection is moot in view of the amendment to claim 6.

CONCLUSION

Applicants submit that the claims are in condition for allowance.

The fee in the amount of $120 for the one month extension fee is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 06275-517US1 / 101307-1P US.

Respectfully submitted,

Date: May 15, 2008

/John T. Kendall/
John T. Kendall, Ph.D.
Reg. No. 50,680

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

APPENDIX A

HUMAN RECOMBINANT CCR1 BINDING ASSAY

Methodology

Membranes
HEK293 cells, from ECACC, stably expressing recombinant human CCR1 (HEK-CCR1) were used to prepare cell membranes containing CCR1. The membranes were stored at -70°C. The concentration of membranes of each batch was adjusted to 10% specific binding of 33 pM [^{125}I] MIP-1α.

Binding assay
100 µL of HEK-CCR1 membranes diluted in assay buffer pH 7.4 (137 mM NaCl (Merck, Cat No 1.06404), 5.7 mM Glucose (Sigma, Cat No G5400), 2.7 mM KCl (Sigma, Cat No P-9333), 0.36 mM NaH_2PO_4 x H_2O (Merck, Cat No 1.06346), 10 mM HEPES (Sigma, Cat No H3375), 0.1% (w/v) Gelatine (Sigma, Cat No G2625)) with the addition of 17500 units/L Bacitracin (Sigma, Cat No B1025) were added to each well of the 96 well filter plate (0.45 µm opaque Millipore cat no MHVB N4550). 12 µL of compound in assay buffer, containing 10% DMSO, was added to give final compound concentrations of $1x10^{-5.5}$-$1x10^{-9.5}$ M. 12 µl cold human recombinant MIP-1α (270-LD-050, R&D Systems, Oxford, UK), 10 nM final concentration in assay buffer supplemented with 10% DMSO, was included in certain wells (without compound) as non-specific binding control (NSB). 12 µl assay buffer with 10% DMSO was added to certain wells (without compound) to detect maximal binding (B0).
12 µL [^{125}I] MIP-1α, diluted in assay buffer to a final concentration in the wells of 33 pM, was added to all wells. The plates with lid were then incubated for 1.5 hrs at room temperature. After incubation the wells were emptied by vacuum filtration (MultiScreen Resist Vacuum Manifold system, Millipore) and washed once with 200 µl assay buffer. After the wash, all wells got an addition of 50 µL of scintillation fluid (OptiPhase "Supermix", Wallac Oy, Turko, Finland). Bound [^{125}I] MIP-1α was measured using a Wallac Trilux 1450 MicroBeta counter. Window settings: Low 5-High 1020, 1-minute counting/well.

Calculation of percent displacement and pIC_{50}

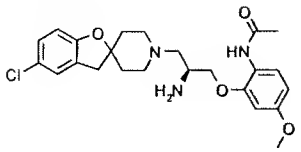
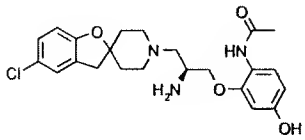
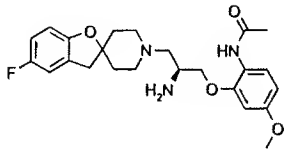
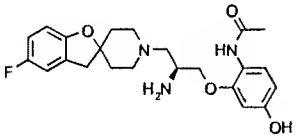
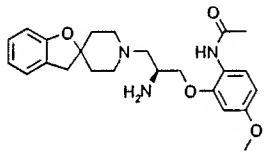
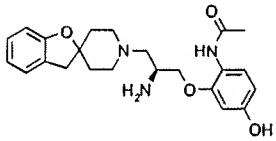
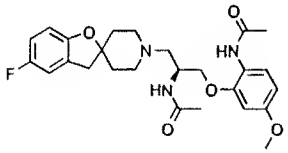
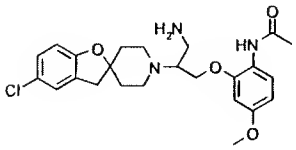
The following equation was used to calculate percent displacement.
Percent displacement = 1- ((cpm test – cpm NSB) / (cpm B0- cpm NSB)) where

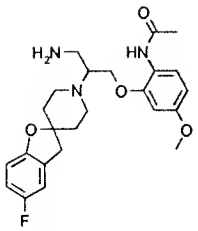
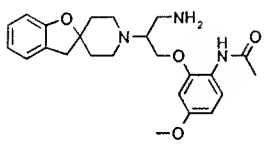
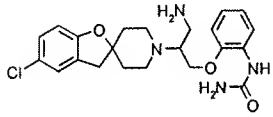
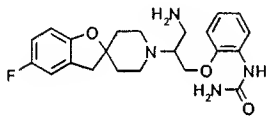
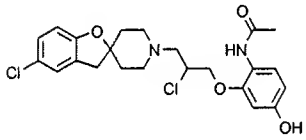
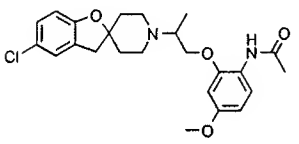
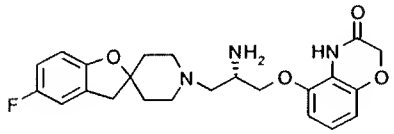
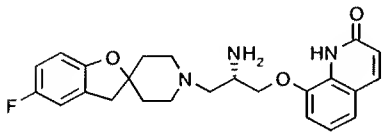
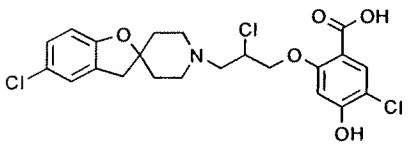
cpm test = average cpm in duplicate wells with membranes and compound and [^{125}I] MIP-1α cpm

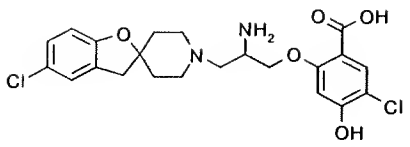
NSB = average cpm in the wells with membranes and MIP-1α and [^{125}I] MIP-1α (non-specific binding) cpm

B0 = average cpm in wells with membranes and assay buffer and [^{125}I] MIP-1α (maximum binding).

The molar concentration of compound producing 50% displacement (IC_{50}) was derived using the Excel-based program XLfit (version 2.0.9) to fit data to a 4-parameter logistics function.

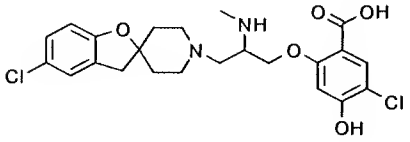
Example No.	Structure	CCR1 IC50 uM
1		0.0063
2		0.00079
3		0.0089
4		0.0014
5		0.032
6		0.018
7		1.8
8		>3.2

9		2
10		>3.2
11		>3.2
12		>3.2
13		0.05
14		2.5
15		0.079
16		0.56
17		0.14



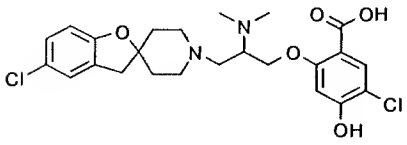
1.3

18



1.4

19



0.25

20